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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,025	10/24/2003	Suzanne M. Torontali	HO-P02882US0 (9394L)	1757

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EXAMINER	
SKIBINSKY, ANNA	

ART UNIT	PAPER NUMBER
1631	

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06/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/693,025	TORONTALI ET AL.
	Examiner	Art Unit
	Anna Skibinsky	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 23 March 2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) 19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendments to claims 1, 12, 15, 16, 17 and 18 are acknowledged. Claims 1-18 are under consideration.

Claim Election/Restriction

1. Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group II, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/18/2006.

Claim Rejections - 35 USC § 112-2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 16-18 recites a composition comprising fluorescent detectable microspheres in lines 1-8 but also recites a method step of identifying said microspheres via flow cytometry lines in 9-10. The metes and bounds of this claim are unclear because both a composition and method step are recited. Clarification is required. Claims 17-18 are also rejected due to being dependent from claim 16 which is indefinite.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (US Pub 2001/0041335) in view of Schwartz et al. (US Patent 4,609,689).

6. Claim 1 recites an identifiable fluorescent detectable microsphere coupled with a pre-optimized oligonucleotide to form an oligonucleotide/target complex. The complex comprises a detectable signal through the binding of a receptor to the label. Furthermore, a labeled ligand is provided for the receptor wherein when the ligand binds to the receptor, the signal is amplified.

7. Goldberg et al. teach providing a surface of nucleic acid probes (i.e. oligonucleotides) and contacting each nucleic acid probe with a nucleic acid target. To permit each nucleic acid target to hybridize to each nucleic acid probe (col. 3, lines 45-65), as in claim 1, step (a). Goldberg et al. further teach a receptor such as avidin or strepavidin, bound to a ligand, such as biotin (col. 3, lines 6-20), and a target polynucleotide that is labeled with a ligand and a receptor (Abstract, lines 4-13) as in claim 1, steps (b) and (c). The ligand can be contacted with a labeled receptor, thus providing a labeled ligand for the receptor as in claim 1, steps (c). The oligonucleotide can hybridize to a DNA sequence with the reverse compliment sequence to form an oligonucleotide/target polynucleotide complex (col. 6, line 67 to col. 7, line 3). The method of the invention is to detect target molecules through a detectable signal (Abstract, lines 1-4 and 22-26). Glodberg et al. also teach quantifying the amplified labeled ligand (col. 3, lines 7-10 and col. 12, lines 49-54), using streptavidin-phycoerythrin (Example 1) where fluorescence is measured (i.e. quantified) before and after antibody amplification (col. 20, lines 19-27 and Table 1), as required in claim 1, step (d) and claim 16.

8. Goldberg et al. do not teach an identifiable fluorescent detectable microsphere linked as required by claim 1, step (a) and identifying the microsphere via flow cytometry, as required by claim 1, step (d). However, Schwartz et al. teaches fluorescently detectable microbeads that are used with flow cytometery and can be quantified using flow cytometery wherein the emission spectra from the beads is

detected (col. 1, lines 15-28). The microbeads are contacted with a polymerizable monomer having a reactive functional group (col. 2, lines 25-50).

9. Claims 2, 3, 6 and 7 recite a pre-optimized oligonucleotide that is selected with an algorithm wherein the one perfect match pre-optimized oligonucleotide has an acceptable measure of correlation with a standard gene expression value, or based on mismatched criteria.

10. Goldberg et al. teach the average difference in intensity detected between matches and mismatches (as required in claims 2 and 3, step (a), (b), (c) or (c)) and values corresponding to signal to noise ratio, number of spikes detected and percent false negatives (col. 21, lines 1-33 and Table 1), and standard deviation is shown in column 9 of Tables 1 and 2.

11. Claims 4, 5, and 12 recite providing a sample of target RNA polynucleotides for more than one gene, subjecting the sample to an array of oligonucleotides that hybridize to more than one different RNA polynucleotide and provide a detectable hybridization finger print for more than one gene that can be identified.

12. Goldberg et al. teach a matrix (col. 3, lines 21-32) and RNA targets synthesized from (col. 11, lines 45-63) the PCR amplification of a plasmid library (col. 18, lines 43-48) to be used in the method of detectable hybridization on a biological chip.

13. Goldberg et al. teaches 10.0 micrograms/ml of molecular probes (col. 18, lines 5-10) as required by claim 8.

14. Claims 9 and 10 recite a ligand that comprises an antibody and a label that is a fluorescent label, chemical, enzyme or gold label. Goldberg et al. teaches ligand (i.e.

biotin) comprising an antibody (col. 3, lines 7-10) as required by claim 9, and ligands that include antibodies (col. 10, lines 53-67) and labels at include fluorescent, gold, or enzymatic labels (col. 12, lines 18-23).

15. Claim 11 recites the label of the target polynucleotide and the ligand are identical. Goldberg et al. teach that the label may be provided on the amplification reagent, or the binding ligand (col. 12, lines 18-23). Once the polynucleotide and ligand complex if formed (Abstract), the label is shared by both polynucleotide and ligand and is thus the same as required by claim 11.

16. Claims 14, 15, 17 and 18 require that the oligonucleotides on the microspheres be different and be complimentary to the same RNA polynucleotide.

17. Goldberg et al. teach an array of different nucleic acid probes immobilized on the surface (col. 4, lines 57-63 and col. 15, lines 9-22) and screening large numbers of RNA targets complementary to the probes (col. 11, lines 45-63 and col. 16, line 58-67).

18. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the method of hybridizing the oligonucleotide with a polynucleotide attached to a receptor and measuring the amplified labeled ligand as taught by Goldberg et al. with the method of using flow cytometery and fluorescent microbeads as taught by Schwarz et al. One of skill in the art would have been motivated to use fluorescent microbeads and quantify the labeled ligand signal via flow cytometery because Schwartz et al. teaches that flow cytometery is used for the rapid detection, measurement, counting and separation of the agent attached to the microbead and that it is the preferred method for the rapid detection and

measure of a variety of cellular constituents and fluorescent microbeads are useful the separation of particles with flow cytometery (Schwartz et al., col. 1, lines 15-41). One of skill in the art would have had a reasonable expectation of success of using flow cytometery to count fluorescent microbeads with an attached ligand because Schwartz et al. teaches the detection of microbeads using flow cytometry while Goldberg et al. teaches microbeads with oligonucleotides attached.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (US Pub 2001/0041335) in view of Schwartz et al. (US Patent 4,609,689), as applied to claims 1-12 and 14-18 above, and further in view of Mirkin et al. (US Patent 6,582,921),

19. Goldberg et al. in view of Schwartz make obvious an oligonuceotide/polynucleotide complex with a receptor and ligand but do not teach RNA polynucleotides that are comprised in a mRNA containing sample and a method for providing mRNA expression profiling information, as required by claim 13.

20. Mirkin et al. teach a plurality of microspheres having oligonucleotides attached where the oligonucleotide sequences have a sequence complimentary to the sequence of the nucleic acid and are labeled with a fluorescent molecule (col. 6, lines 48-52). Furthermore, the nanoparticle microspheres and polynucleotides can form larger microsphere complexes (Figure 18; and col. 16, line 66 to col. 17, line 4). The method of the invention provides a way of detecting RNA, which is the target polynucleotide (col. 21, lines 51-61). Mirkin et al. teach that the detected RNA include mRNA (col. 21, lines

51-61) and that nucleic acids may be detected in samples of solutions with PCR containing components (col. 22, lines 19-32).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the method of labeled oligonucleotide/polynucleotide RNA sequences and receptors bound to fluorescent microspheres of Goldberg et al. in view of Schwartz et al. with the binding of RNA which is mRNA as taught by Mirkin et al. One of skill in the art would have been motivated to study mRNA using the method of fluorescent microspheres of Goldberg et al. in view of Schwartz et al. because detection of mRNA is linked with the diagnosis and monitoring of diseases (Mirkin et al., col. 21, lines 50-67). Goldberg et al. and Mirkin et al. both teach a hybridization detection method where oligonucleotides bind to polynucleotides, thus one of skill in the art would have had a reasonable expectation of success at producing the microsphere oligonucleotide/polynucleotide complex where the polynucleotide is mRNA.

Response to Arguments

21. Applicant's arguments filed 3/23/2006 have been fully considered but they are not persuasive.

22. Applicants argue (Remarks, page 8, lines 15-18) that Mirkin et al. fail to teach an identifiable fluorescent detectable microsphere which is used within the flow cytometer and read by a two laser system.

23. In response, Schwartz et al. teaches detection of fluorescent microbeads with flow cytometery. It is further noted that a two laser system is not a limitation recited in the instant claims.

24. Applicants argue (Remarks, page 8, lines 18-20) that the prior art does not teach "exciting fluorophores within the bead".

25. In response, the instant claims recite "fluorescent detectable microspheres" which do not require that the fluorophore be WITHIN the microbead. The instant disclosure defines a microsphere [paragraph 0025] as having a detectable signature **on** or in the structure. Schwartz et al. teaches detection of fluorescent microbeads with flow cytometery.

26. Applicants argue (page 8-9, connecting sentence) that flow cytometery was originally developed for the utilization of protein and not oligonucleotides and that Goldberg and Mirkin would not have thought to employ a flow cytometry as part of the methodology of their invention.

27. In response, it is noted that Mirkin does, in fact, teach attachment of nucleotide sequences to beads while Schwartz et al. provide motivation for the use of flow cytometery to detect such beads by teaching that it is the preferred method for the rapid detection and measurement of a variety of cellular constituents (col. 1, lines 15-17).

Conclusion

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

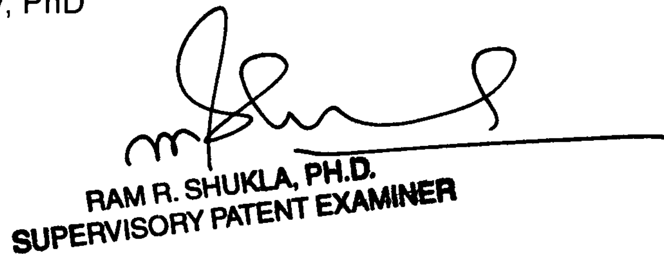
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anna Skibinsky, PhD



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